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Therapeutic Anti-Angiogenesis for Malignant Brain Tumors

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Key Words

Angiogenesis · Brain tumor · Metastases · Clinical trial

Summary

Malignant brain tumors, especially malignant gliomas, have a poor prognosis, a fact which has remained unchanged over the last decades despite the employment of multimodal therapeutic approaches. Malignant gliomas are among the most vascularized tumors known and the amount of vascularization has been correlated to their prognosis. Since tumor growth is dependent on concomitant vascularization, recent experimental studies have focused on the use of anti-angiogenic molecules as a novel strategy in brain tumor therapy. Angiogenesis inhibitors target at proliferating endothelial cells and suppress the formation of a sufficient vascular bed. Inhibitors such as TNP-470, suramin and angiostatin have shown their therapeutic potential in experimental studies. In a clinical setting, they could be applied for the treatment of multiple tumors or postsurgically as an adjuvant therapy to prevent recurrence. This article discusses presently available anti-angiogenic agents, emphasizing on substances already in clinical trials.

Schlüsselwörter

Angiogenese · Hirntumoren · Metastasen · Klinische Studien

Zusammenfassung

Maligne Hirntumoren, insbesondere die malignen Gliome, haben trotz multimodaler Therapieansätze eine unverändert schlechte Prognose. Diese Aggressivität korreliert mit der Tatsache, daß maligne Gliome zu den gefäßreichsten Tumoren zählen, die wir kennen. Die Quantifizierung der Gefäßdichte in diesen Tumoren erlaubte die Korrelation zur Überlebenszeit der Patienten. Da das Tumorwachstum von einer begleitenden Neovaskularisierung abhängt, wurden erste experimentelle Therapieansätze durchgeführt, um das Tumorwachstum durch Inhibierung der Neovaskularisierung zu verhindern. Inhibitoren der Angiogenese, z.B. TNP-470, Suramin und Angiostatin hemmen die Proliferation von Endothelzellen und die Ausbildung eines funktionsfähigen Gefäßbettes. Erste experimentelle Ansätze haben ihre tumorstatische Wirksamkeit in vivo bewiesen. Zur klinischen Behandlung wären diese Substanzen in Verbindung mit bestehenden Therapien einsetzbar, insbesondere für die Behandlung multipler Tumoren und zur postoperativen Therapie. Diese Übersichtsarbeit beschreibt die neuesten anti-angiogenen Therapiekonzepte besonders mit Hinblick auf Substanzen, die in ersten klinischen Studien eingesetzt werden.

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Introduction

It is well recognized that angiogenesis is essential for tumor growth and development of metastasis. With the exception of avascular leptomeningeal tumor spread, tumors cannot grow beyond a certain size without concurrent extension of their vascular bed. Most current treatment concepts aim at the neoplastic cell compartment and rely on cytoreductive measures. On the contrary, anti-angiogenic treatment focuses on the endothelial cell compartment. Endothelial cells are recruited by solid tumors from the existing vasculature and from endothelial precursor cells. Tumor-associated endothelial cells are non-neoplastic cells although they exhibit some features of malignancy such as proliferation and invasiveness. While heterogenous tumors are prone to resistance through clonal selection, endothelial cells represent a homogenous non-neoplastic cell compartment that is less likely to be subject to resistance. Endothelial cells line the inner part of blood vessels and are easily accessible for circulating drugs, especially in comparison to tumor cells. With special respect to brain tumors, endothelial cells can be targeted independently of the blood-brain barrier.

Solid tumors cannot grow beyond a size of 1–3 mm in diameter without acquisition of new blood vessels, thus inhibition of angiogenesis would be sufficient to keep a majority of intracerebral solid tumors asymptomatic.

Brain tumors are among the most highly vascularized tumors known [1]. Li et al. [2] in 1994 reported a correlation of microvessel grading with cerebrospinal fluid levels of basic fibroblast growth factor (bFGF), and with the risk of recurrence of death in a variety of pediatric brain tumor types. Leon et al. [3] in 1996 reported a negative correlation between increasing microvessel counts and disease-free survival. They demonstrated that vascularity represents an independent prognostic indicator.

The forementioned data show that tumor-related vessel growth represents an attractive new therapeutic target. A number of anti-angiogenic treatment strategies have been developed and will be discussed.

Positive Regulators of Angiogenesis

Angiogenesis is a complex multifaceted biological process and, thus, offers potential therapeutic targets at multiple levels. After neoplastic transformation of a normal cell has occurred, proliferation ensues. As long as proliferation and cell death remain balanced, the tumor does not expand nor does it need in-growing vessels [4]. This dormant state is of variable duration and ends as soon as angiogenic signals are released and neovascularization ensues, this phenomenon is referred to as the angiogenic switch. Angiogenic growth factors produced by tumor cells induce endothelial cell proliferation. Along with the properties of the surrounding matrix, growth factors determine the success of tumor-related angiogenesis and endothelial cell recruitment. A growing number of molecules with angiogenic properties produced by tumor cells as well as endothelium-specific angiogenic molecules have been identified. While a comprehensive list is given in table 1, this overview focuses mainly on molecules that are already subject of clinical investigation.

Table 1. Angiogenic factors

Vascular endothelial growth factor (VEGF)
Acidic and basic FGF (aFGF, bFGF)
Transforming growth factor alpha and beta (TGF-α and -β)
Angiogenin
Epidermal growth factor (EGF)
Scatter factor / HGF
Placenta-derived growth factor (PlGF)
Interleukin-8 (Il-8)
Tumor necrosis factor (TNF)
Insulin-like growth factor (IGF)
Platelet derived growth factor (PDGF)
Prostaglandins E_1 and E_2
Androgen, estrogen
Angiopoietin-1 (ANG-1)
ANG-2 in the presence of VEGF

VEGF and VEGF Receptors

Vascular endothelial growth factor (VEGF) represents an important signal molecule during initiation and maintenance of angiogenesis by hypoxia [5]. The VEGF receptors belong to a family of endothelial receptor tyrosine kinases which are activated upon high-affinity binding of the growth factors to their cognate receptors. VEGF and its receptors are expressed at high levels in many types of human tumors, including gliomas [6], where they exhibit a cell-type specificity [7]. Whereas VEGF is secreted by tumor cells as well as by normal tissue in response to hypoxia, the VEGF receptor KDR/flk-1 is expressed on the surface of activated endothelial cells, especially at tumor sites [8]. Forced overexpression of VEGF by tumor cells has been shown to enhance their tumorigenic potential [5, 9]. The cellular effects of VEGF are mediated by at least three different receptors VEGF-R-1, -2, and -3, also termed flt-1, flk-1/KDR, and flt-4, respectively. In addition, VEGF expression has been shown to represent an independent prognostic factor for the outcome of pancreatic, ovarian, and mammary ductal carcinoma in situ, as well as of metastasizing testicular cancer and of brain tumors [10].

In brain tumors, VEGF was shown to be overexpressed in gliomas compared to normal tissue [7, 10, 11]. Furthermore, expression of VEGF has been reported to correlate with microvessel density in gliomas and meningiomas [10]. Consistent with its regulatory role in vessel permeability, VEGF expression also correlates with tumorigenic edema in cerebral metastases, meningiomas, and gliomas [12–15]. Based on immunohistochemical expression data on 162 astrocytic gliomas, VEGF expression has been correlated with overall survival

Table 2. Angiogenesis inhibitors in clinical trials

Drug	Trial	Mechanism	Company
Marimastat	phase III	synthetic inhibitor of MMPs	British Biotech
AG-3340	phase II + III	synthetic inhibitor of MMP-2/-9	Agouron
COL-3	phase I + II	synthetic inhibitor of MMPs	Collagenex
Neovastat	phase I + II	endogenous inhibitor of MMPs	Aeterna
BMS-275291	phase I	synthetic inhibitor of MMPs	Bristol-Myers Squibb
CGS-27023A	phase I + II	synthetic inhibitor of MMPs	Novartis
Bay-12–9566	phase III	synthetic inhibitor of MMP-2 /-9	Bayer
TNP-470	phase I + II	Fumagillin-analogue	TAP pharmaceuticals
Thalidomide	phase I + II + III	inhibits EC proliferation; inhibits EC activation via monocyte by TNFα blockade	Celgene
Squalamine	phase I + II	extract from shark liver; inhibits sodium-hydrogen exchanger, NHE3	Magainin Pharmaceuticals
Combrestatin A-4 prodrug	phase I + II	apoptosis of endothelial cells	Oxigene
Endostatin	phase I	inhibits endothelial proliferation	Entremed
Angiostatin	phase I	inhibits EC proliferation	Entremed
SU5416	phase I + II + III	blocks VEGF receptor signaling	Sugen
SU101	phase III	blocks PDGF receptor signaling	Sugen
SU6668	phase I	blocks VEGF, FGF, PDGF receptor signaling	Sugen
Interferon-a	phase II + III	inhibition of bFGF, VEGF, and MMP-9 production	Multiple vendors
Interferon-ß	phase II + III	inhibition of endothelial cell migration and morphogenesis	Multiple vendors
Anti-VEGF Ab	phase I + II	humanized monoclonal antibody to VEGF	Genentech
EMD121974	phase I	blocks $\alpha_v\beta_3$ integrins on EC	Merck KcgaA Darmstadt
CAI	phase I + II + III	inhibits Ca++ influx	National Cancer Institute, USA.
Interleukin-12	phase I + II	upregulation of interferon-γ and IL-10	Genetics Institute
IM-862	phase I + II + III	upregulates IL-12; inhibits VEGF and bFGF production	Cytran
IMC-C225	phase I + II + III	humanized monoclonal antibody to the EGF receptor	ImClone
IMC-1C11	phase I	humanized monoclonal antibody to the VEGF receptor KDR	ImClone
Vitaxin	phase I	humanized monoclonal antibody to the $\alpha_v\beta_3$ integrin	MedImmune / Ixsys
Anti-VEGF Ab	phase II + III	humanized monoclonal antibody to VEGF	Genentech
Suramin	phase II	prevents PDGF binding	Multiple vendors
Troponin-I, BLS 0597 (fragment of troponin I)	phase I	inhibits EC proliferation, binds ATP synthase	Boston Life Sciences
Angiozyme	phase I	ribozyme degrades VEGF mRNA	Ribozyme
PTK787 / ZK-222584	phase I	specific inhibitor of FLK-1 and KDR receptor for VEGF	Novartis, Schering
Pentosan polysulfate	phase I	downregulates bFGF production	Georgetown University, Washington
ZD-0101	phase I + II	endotoxin binds to EC and induces antiinflammatory response	AstraZeneca / CarboMed
CM-101		VEGF and VEGF-R2 downregulation	

but was not shown to be an independent prognostic factor in gliomas [16]. In low-grade astrocytomas, however, VEGF expression correlates with the outcome [17].

Several lines of experimental evidence suggest that targeting VEGF may lead to highly effective anti-angiogenic treatment. Thus, antibodies against VEGF, VEGF-R, and VEGF-diphtheria toxin conjugates exert an inhibitory effect on the growth of tumor xenografts in mice [18–20]. The retroviral introduction of VEGF antisense-RNA into glioma cells in a mouse model resulted in the inhibition of tumor growth and prolongation of survival time [21]. A 16 kDa prolactin fragment has been demonstrated to interfere with VEGF-induced signalling pathways by inhibiting phosphorylation of two mitogen-activated protein kinases (MAPK) by VEGF [22]. Whether this endogenously produced anti-angiogenic molecule can be employed for therapeutic use remains to be investigated.

Antibodies against human VEGF and VEGF receptors are currently being tested in phase II/III clinical trials (table 2). While some of the recently reported VEGF-R antagonists such as the porphyrin antagonist TMPP or short peptides identified by phage display have not yet reached the clinical arena, other low-molecular-weight inhibitors of VEGF-R tyrosine kinases such as SU5416, SU6668, PTK787, and ZD4190 are already under clinical investigation (table 2).

Tie – Receptors and Angiopoietins

Tie-1 and Tie-2, tyrosine kinases with immunoglobulin and epidermal growth factor homology domains, resemble the VEGF receptors in that they constitute endothelial-cell-spe-

Table 3. Endogenous inhibitors of angiogenesis

Interferons, esp. interferon-α and -ß
PF4 (platelet-derived factor 4)
Thrombospondin-1
Metallospondin
TIMPs (tissue inhibitors of metalloproteinases)
Plasminogen activator/inhibitor
ANG-2 (angiopoietin-2) in absence of VEGF
SPARC (secreted protein, acidic and rich in cysteine)
Angiostatin (cleaved from plasminogen)
Endostatin (cleaved from collagen XVIII)
PEX (cleaved from MMP-2)
N-terminal fragment of anti-thrombin III
16-kDa fragment of prolactin
Tn-1 (cleaved from Troponin-1)
Vasostatin (cleaved from calreticulin)
AaAT111 (cleaved from ATIII)
Arresten (cleaved from collagen type IV)
Canstatin (cleaved from collagen type IV)
Restin (cleaved from collagen type XV)
N-terminal fragment of platelet factor 4
Proliferin-related protein (cleaved from proliferin)

cific surface receptors with tyrosine kinase activity. The physiologic function of Tie receptors and their ligands, called angiopoietins (ANG), in angiogenesis has only recently been elucidated. ANG-1, the major physiologic activator of Tie-2, promotes blood vessel maturation and stability. ANG-2 counteracts this effect by competitively inhibiting the binding of ANG-1 to Tie-2. Knock-out mice lacking the Tie receptors did not survive beyond embryonic stages [23]. While Tie-$1^{-/-}$ mice failed to establish the structural integrity of vascular endothelial cells leading to localized hemorrhage, Tie-$2^{-/-}$ mice displayed significant abnormalities in growth and organization of the vasculature [23]. Upregulation of ANG-2 by hypoxia occurs in endothelial cells in vitro and in vivo [24]. Counteracting VEGF-induced permeability, ANG-1 functions as an anti-permeability factor when administered chronically during vessel formation [25, 26].

Expression of ANG-1 or ANG-2 has not been detected in normal brains. However, upregulation of Tie-2-receptor mRNA and ANG-2 mRNA was demonstrated in endothelial cells of glioma vasculature, while ANG-1 was found to be upregulated in glioma cells suggesting a role for angiopoietins in glioma angiogenesis [27–29]. Application of the soluble extracellular domain of Tie-2-inhibited angiogenesis in the rat cornea, as well as tumor growth in a skin window chamber [30]. Adenoviral delivery of a recombinant, soluble Tie-2 receptor suppressed murine mammary carcinoma or melanoma growth and development of metastasis in mice [31].

Integrins and Matrix Metalloproteinases

Invasion and migration requires a complex interaction between tumor cells and extracellular matrix (ECM) components. Tumor cell invasion involves cell-matrix adhesion, chemotaxis, cell migration and proteolysis. Endothelial cells interact with ECM proteins such as fibronectin via specific receptors expressed on their cell surface. They eventually invade and dissolve the basement membrane and the surrounding matrix by secretion of enzymes. This proteolytic degradation of the ECM plays a central role in cancer invasion as well as in non-neoplastic remodeling processes. The integrin family of heterodimeric glycopeptides, particularly $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins, serve as major receptors for ECM-mediated cell adhesion and migration. $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins have been demonstrated to be upregulated during repair, retinal neovascularisation, and tumor neo-angiogenesis [32, 33]. $\alpha_v\beta_3$ integrins are expressed in small blood vessels of glioblastoma [34]. Antibodies to a variety of integrins have been shown to inhibit matrigel invasion of glioma cell lines and primary cultures [35].

Among the key enzymes which participate in ECM degradation are the metalloproteases (MMP), zinc-binding endopeptidases such as MMP-2 and MMP-9, and serine proteases such as tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA). MMPs are secreted as inactive proenzymes and become activated at the site of action, e.g. the tumor cell. An imbalance between MMPs and their naturally occurring inhibitors, so-called tissue inhibitors of metalloproteinases (TIMP) has been observed in a variety of tumors, including brain tumors [36–39]. The serine proteases, tPA and uPA, activate the proenzyme plasminogen to plasmin, which in turn is responsible for fibrinolytic activity. Consistent with their role in cancer spread, elevated levels of both enzymes have been associated with poor prognosis in a variety of tumors.

Matrix metalloproteinase-2 and integrin $\alpha_v\beta_3$ are functionally associated on the surface of angiogenic blood vessels. MMP-2 (also called collagenase IV or gelatinase A) has been shown to cleave type IV collagen, the major structural component of basement membranes, with high specificity. Moreover, the metastatic potential of tumor cells has been correlated with the activity of this enzyme [40]. Short peptides which target MMP-2 and MMP-9 inhibited the migration of human endothelial and tumor cells and improved survival of mice bearing human tumors [41]. Synthetic MMP inhibitors such as Marimastat, Batimastat, AG3340, Bay 12–9556, and others are already subject of clinical trials.

Endogenous Inhibitors

Only recently we have witnessed the discovery of a number of naturally occuring endogenous inhibitors of angiogenesis. Besides primarily anti-angiogenic molecules such as platelet-derived factor 4, or thrombospondin-1, a growing number of anti-angiogenic factors such as angiostatin and endostatin represent proteolytic fragments of proteins with various functions that may be unrelated to angiogenesis (table 3).

Thrombospondin

Activated platelets, endothelial cells, and fibroblasts release several thrombospondin isoforms (TSP 1–4), a 450-kD homotrimeric glycoprotein with a broad tissue distribution. TSP-1 and TSP-2 were shown to inhibit endothelial cell proliferation, angiogenesis, and tumor growth [42, 43]. The p53 gene, a major cell cycle regulator and tumor-suppressor gene, was proposed to inhibit angiogenesis by regulation of TSP-1 synthesis [44]. This finding is of special interest, as loss of p53 is a common event in human cancer, especially in glioma. Upon introduction of a wild-type chromosome 10 into 3 human glioblastoma cell lines, their ability to form tumors in nude mice was lost and an anti-angiogenic phenotype was acquired [45]. Although chromosome 10 harbors a number of potential tumor-suppressor genes, including the PTEN gene, the observed change in angiogenesis was thought to be attributable to the induction of thrombospondin-1 secretion, because a neutralizing thrombospondin antibody completely relieved the inhibition [45]. Similarly, thrombospondin-2 was shown to be a potent inhibitor of angiogenesis and tumor growth in mice after transfection into squamous cell carcinoma cells, although its expression did not alter tumor cell proliferation or apoptosis in vitro [43]. Moreover, the combined overexpression of TSP-1 and TSP-2 completely prevented tumor formation in this model [43]. Recently, short peptide fragments originating from the TSP protein have been shown to exhibit similar anti-angiogenic properties and, thus, represent potential candidates for the use in anti-angiogenetic therapy [46, 47].

Angiostatin

The discovery of the first highly specific anti-angiogenic molecule, termed angiostatin, by O'Reilly et al. [48] has highlighted the central role of angiogenesis in tumor development. This initiated a search for new endogenous inhibitors of tumor-related angiogenesis. The search for an endogenous inhibitor of tumor growth was based on the observation that metastases began to grow after the removal of the original solid tumor. When serum and concentrated urine from Lewis lung cell (LLC) carcinoma bearing mice were given to mice that had undergone removal of a solid LLC, a significant suppression of metastases was observed suggesting the presence of a soluble growth inhibitory mediator in these fluids. Interestingly, serum and urine from LLC-bearing mice inhibited endothelial cell proliferation, but had no effect on tumor cell proliferation in vitro. The purified mediator, termed angiostatin, was identified as a 38-kDa amino-terminal fragment of plasminogen spanning the first 4 kringle domains of plasminogen [48]. Further investigations have shown that kringles 1–3 harbour the endothelial cell inhibitory function, whereas kringle 4 had little effect [49, 50]. However, a longer plasminogen fragment encompassing kringles 1–5 is also an effective inhibitor of endothelial cells and of tumor growth [51]. The observation of angiostatin-induced apoptosis of endothelial but not of tumor cells, indicates that endothelial cells and endothelial precursor cells are exclusive cellular targets of angiostatin [48, 52]. In addition, angiostatin has been shown to inhibit endothelial cell migration and invasion, as well as tube formation in vitro [50, 53]. Angiostatin therapy keeps LLC lung metastases in a dormant state which is characterized by insufficient vascularisation and high proliferation balanced by a high apoptotic rate [4, 48, 54]. Subcutaneous and intracerebral gliomas of both rat and human origin were successfully treated in a nude mouse model by systemic administration of angiostatin [55, 56]. In addition, retroviral or adenoviral transduction of the angiostatin gene into established brain tumors in mice inhibited tumor growth effectively [57, 58]. To date, many other extracerebral tumor types have been demonstrated to respond with growth inhibition to systemic application of angiostatin in vivo [4, 48, 54]. Furthermore, the administration of angiostatin in conjunction with ionizing radiation resulted in synergistic effects of the two modalities in 4 different cancer types in mice including mouse LLC, human prostate and larynx squamous cell carcinomas, as well as human D54 glioma [59, 60].

Endostatin

Using an experimental approach similar to that used for the isolation of angiostatin, O'Reilly et al. [61] isolated endostatin, a 22-kDa carboxy-terminal fragment of collagen XVIII α1, from a murine hemangioendothelioma. Similarly to angiostatin, it acts anti-angiogenic by induction of apoptosis and specific inhibition of proliferation, migration, and tube formation of endothelial cells [61–63]. Endostatin has successfully been used systemically or by gene transfer to treat a variety of cancers including fibrosarcoma, melanoma, hemangiothelioma, prostate, renal, mammary, lung, and colon carcinoma [61]. Treatment of mice carrying fibrosarcoma, melanoma or LLC with exogenously administered endostatin for several cycles resulted in a permanent size reduction of tumors into small, dormant nodules [64]. The combined application of angiostatin and endostatin has shown synergistic effects on tumor suppression indicating that the molecular targets differ between the two inhibitory molecules [65]. Recombinant endostatin is currently subject of clinical trials for a variety of cancers (table 2).

Synthetic Anti-Angiogenic Factors

Suramin

Suramin was initially introduced 80 years ago as a potent antitrypanozomal agent. Only recently, it was shown to inhibit binding of platelet derived growth factor (PDGF) to its receptor by binding to PDGF directly [66]. Thus, suramin acts anti-angiogenic by disrupting the PDGF feedback loop operating in many tumors, including brain tumors [67]. Suramin was also shown to inhibit VEGF-induced tyrosine phosphorylation of KDR in intact cells and to suppress bFGF-induced angiogenesis, tube formation, and matrigel invasion [68]. Its growth sup-

pressive properties have been demonstrated for a number of tumors including glioma and meningioma [69–72]. Suramin is under clinical investigation (table 2).

Fumagillin and TNP 470

Fumagillin is a secreted antibiotic of the fungus *Aspergillus fumigatus*. Its inhibitory property on endothelial cell proliferation was first noted in contaminated endothelial cell culture dishes. Fumagillin was also shown to inhibit tumor-induced angiogenesis in vivo [73]. More potent synthetic derivatives of fumagillin are TNP-470 or AMG-1470 [74]. TNP-470 has been demonstrated to reduce endothelial cell proliferation by inhibition of urokinase-type plasminogen activator [75]. In addition, it acts growth suppressive on hematopoietic progenitor cells [76]. While there are controversial reports on the effects of TNP-470 on growth suppression of tumor cells in vitro, several in vivo experiments have clearly demonstrated its growth-suppressive effect on primary and metastatic tumor growth, including pituitary adenoma, meningioma, medulloblastoma, and glioma [77–82]. TNP-470 has entered clinical trials for a variety of solid tumors including AIDS-associated Kaposi's sarcoma, prostate, cervical and pancreatic cancers, as well as malignant glioma.

Thalidomide

Thalidomide was initially developed as a compound to treat morning sickness and headaches of pregnant women, but has become known for its devastating teratogenic effects. Because of its anti-angiogenic properties it is assumed that inhibition of vascular development during embryogenesis accounts for its teratogenicity [83]. While thalidomide inhibits endothelial cell and tumor cell proliferation in vitro, it has variable inhibitory effects on tumor growth and on the migration of metastases [84, 85]. Thalidomide or its metabolites have been demonstrated to repress the transcriptional activity of genes encoding growth factors and integrins by binding to regulatory promoter sequences. In addition, it was shown to interact synergistically with other chemotherapeutic drugs in vivo. A recent phase II study on the effects of thalidomide in advanced melanoma, renal cell, ovarian and breast cancer has revealed only modest therapeutic effects in renal cell carcinoma with the other tumor types remaining unaffected [86]. However, thalidomide has shown considerable effects even as a single agent in patients with multiple myeloma and hepatocellular carcinoma [87, 88]. Clinical trials for AIDS-related Kaposi sarkoma and other types of cancer are being conducted. The findings of a recently conducted phase II trial on Thalidomide in patients with high-grade gliomas demonstrated low toxicity and only minor responses to treatment [89].

Conclusion

The promising experimental data on anti-angiogenic intervention in the treatment of cancer, both in vitro and in vivo, for the treatment of experimental primary brain tumors and for metastases warrant clinical investigation of anti-angiogenic substances in human cancer. Compared to conventional chemotherapeutics, anti-angiogenic substances have less toxic side effects and are less likely to develop drug resistance. Especially with regard to the highly vascularized glioblastoma that still carries a dismal prognosis, anti-angiogenic strategies may offer new hope. In a clinical setting therapeutic anti-angiogenesis could be applied pre-surgically for devascularization, post-surgically to prevent recurrence of microscopic residual tumor with or without the combination of established cytotoxic drugs or radiation therapy.

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